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Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus is a chronic disease that has been increasing in prevalence in the United States every year. Diabetes is associated with numerous physical health complications, most notably the development of cardiovascular disease. In addition, the financial burden imposed by diabetes is great and includes medical costs and lost work time. Most patients with diabetes take prescription oral anti-diabetic medications (OADs) but still do not have adequate glycemic control. When adequate glycemic control is not achieved with these medications, injectable insulin is then required; it is understandable that patients object to this type of invasive treatment and would prefer to remain on oral therapies. Over-the-counter dietary supplements, specifically chromium picolinate and biotin, have been studied for their efficacy as glycemic control agents; the purpose of this metasynthesis was to review existing literature pertaining to concurrent use of both chromium picolinate and biotin supplements as adjunct therapy to prescription OADs to determine if improved glycemic control is achieved in patients with type 2 diabetes mellitus.

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: diabetes, chromium picolinate and biotin. Relevant articles were assessed for quality using the GRADE system. A search on the NIH clinical trials site revealed there are no trials currently registered relating to the concomitant use of chromium picolinate and biotin in patients with type 2 diabetes mellitus.

Results: Ninety-six articles were reviewed for relevancy; two met inclusion criteria and were included in this systematic review. Both studies included were randomized, double blind, placebo-controlled trials that found a statistically significant improvement in glycemic control with dual chromium picolinate and biotin treatment.

Conclusion: Chromium picolinate and biotin appear to modestly improve glycemic control. Chromium picolinate and biotin are safe, over-the-counter supplements; due to evidence obtained from prior animal studies, the lack of significant adverse drug reactions and modest-to-substantial blood-glucose reducing effects, chromium picolinate and biotin supplementation as adjunct therapy to prescription OADs may be clinically justified.

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Annjanette Sommers, PA-C, MS

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Type 2 diabetes mellitus, chromium picolinate, biotin, glycemic control, human

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Biography

Brandy A. Urbanowicz hails from the mountain town of Gunnison, Colorado. She received a Bachelor of Arts degree from Western State Colorado University in 2012 and majored in Biology with an emphasis on Cell Biology/Pre-Medicine. Prior to PA school she had experience as a volunteer EMT-B and worked as a CNA. After PA school she plans to work in Primary Care in rural communities, in both the United States and abroad.

Abstract

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List of Abbreviations

ADA	American Diabetes Association
ADR	Adverse Drug Reactions
ALT	Alanine Aminotransferase
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
AST	Aspartate Aminotransferase
AUCg	Area Under Curve, glucose
BMI	Body Mass Index
BP	Blood Pressure
CrPic	Chromium Picolinate
CVA	Cerebrovascular Accident
DKA	Diabetic Ketoacidosis
DMT2	Type 2 Diabetes Mellitus
DVT	Deep Vein Thrombosis
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
NIH	National Institute of Health
OAD	Oral Anti-Diabetic Medication
OGTT	Oral Glucose Tolerance Test
OTC	Over the Counter (non-prescription)
PE	Pulmonary Embolism
SD	Standard Deviation
SEM	Standard Error of the Mean
ULN	Upper Limit of Normal
VLDL	Very Low Density Lipoprotein

Chromium Picolinate and Biotin Supplementation May Improve Glycemic Control in Patients with Type 2 Diabetes Mellitus

BACKGROUND

The prevalence of diabetes, especially type 2 diabetes mellitus (DMT2) in the United States has been increasing every year.[1] As of 2011, 8.5%, or almost 20 million of U.S. adults have physician-diagnosed diabetes, with another estimated 11 million adults with undiagnosed diabetes. Of this combined approximate 31 million, 90%-95% have DMT2.[2,3]

The physical complications of diabetes are vast and include, but are not limited to, significant cardiac, hepatic, and renal diseases.[4-11] In addition to the physical health complications, diabetes takes a substantial economic toll. In 2012, total economic burden of diabetes including medical costs, disability, work loss and premature death was estimated at $245 billion.[12] The costs of health complications alone attributable to diabetes is on average $47 240 per patient over 30 years.[13]

Both health and financial consequences can be reduced if patients with diabetes obtain adequate glycemic control. Glycemic control can be obtained through weight loss and careful attention to diet for many,[14] but the majority of overweight or obese people are either unsuccessful complying with a weight loss regimen or are unsuccessful at maintaining any weight lost.[15,16] As a result, most patients with DMT2 take prescription oral anti-diabetic medications (OADs). Approximately 85.6% of patients with diabetes take OADs, insulin, or both.[12] The most frequently used medications reduce glycated hemoglobin (HbA1c) on

average between 1%-2% and are metformin, sulfonylureas, and thiazolidinediones, but they come with numerous adverse drug reactions (ADRs) including diarrhea, lactic acidosis, weight gain, hypoglycemic events, hepatotoxicity, and congestive heart failure.[17-20]

Chromium deficiency has been shown to cause insulin resistance and diabetes,[21] so it has been postulated that chromium supplementation can reverse these conditions.[22,23] Chromium supplementation has been studied as a blood-glucose lowering agent in both animal and human models with mixed results.[23,24] One study[23] found supplemental chromium had little effect lowering blood glucose on the entire study cohort as a whole, but found a significant lowering of HbA1c and increased insulin sensitivity compared to baseline in a cohort subset considered "responders". Another study[25] demonstrated a decreased requirement for exogenous insulin with chromium administration.

In addition to chromium, biotin treatment has been shown to improve insulin resistance and impaired glucose tolerance as well as decrease blood glucose in several animal studies.[26-30] In one study,[27] genetically diabetic mice were given various levels of biotin; after 10 weeks the mice demonstrated lowered post-prandial glucose levels and improved insulin resistance. In three other studies involving diabetic rats, biotin was shown to prevent insulin resistance in skeletal muscle[28] and to improve impaired glucose tolerance.[29,30] More importantly, in a human study, poorly-controlled diabetics showed a significantly improved fasting glucose after receiving biotin for one month.[31] Results of these studies have lead researchers to consider dual treatment with chromium and biotin as adjunct therapy to prescription OADs for glycemic control improvement in patients with DMT2.

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: diabetes, chromium picolinate and biotin. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating the effectiveness of dual therapy with CrPic and biotin for glycemic control improvement in people with DMT2 were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.[32] A search on the NIH clinical trials site revealed no currently registered trials relating to the use of CrPic combined with biotin in patients with DMT2.

RESULTS

The initial result of the search yielded 98 articles for review; 8 from Medline-OVID, 64 from CINAHL and 26 from Web of Science. After screening relevant articles for randomized controlled trials, adult patients with DMT2, human subjects and English language studies, a total of two articles met inclusion criteria.[33,34] Refer to Tables 1 and 2 for the GRADE evaluation and summary of results.

Singer et al study

This is a randomized, double blind, placebo-controlled trial[33] which looked at the effect of oral CrPic and biotin at improving glycemic control in overweight patients with uncontrolled, treated DMT2.[33]

Glycemic control was measured via plasma fructosamine, insulin and fasting glucose levels, area under curve for glucose (AUCg) and oral glucose tolerance test (OGTT)

measured at 30, 60, 90 and 120 minutes. Secondary endpoints were effects on total cholesterol as well as the cholesterol fractions HDL, LDL, VLDL, ApoA, and ApoB, triglycerides and triglyceride:HDL ratio. The trial enrolled 43 subjects at a single study site in the United States.[33]

Eligibility criteria consisted of patients who were overweight or obese classified with a body mass index (BMI) $\geq$25 to $\leq$35 kg/m^2; between the ages of 18 and 65; a diagnosis of DMT2 for $\geq$1 year; poorly-controlled (HbA1c $\geq$7.0%); persistent impaired glucose control (2-h glucose >200 mg/dL); and stable on OADs prior to study entry. OADs allowed were metformin, sulfonylureas, and thiazolidinediones, but the amount and duration of OADs were not controlled for in the study. Exclusion criteria consisted of patients who were currently on or required insulin treatment.[33]

Subjects were assigned 1:1 to either a treatment group in which they received 600 µg Cr^{3+} in the form of CrPic and 2 mg biotin, or a placebo group, with a study length of 30 days. CrPic and biotin were administered as a single capsule manufactured under the name Diachrome® by Nutrition 21, Inc., Purchase, NY. Although the study states it was a randomized, double-blind trial it does not give details pertaining to how randomization or blinding occurred.[33]

Both the treatment group and placebo group were balanced at the beginning of the study with respect to demographics, ie, age, sex, race, weight, height, BMI and blood pressure (BP), as well as baseline HbA1c (p= 0.1430 to 0.9787). Of the 43 randomized patients at the study beginning, seven (16.3%) were either lost to follow-up or excluded for protocol violations; one patient was lost from the treatment group and six lost from the placebo group. Data were collected on 36 patients considered eligible for analysis after these

losses; 20 patients were assigned to the treatment group and 16 patients were assigned to the placebo group.[33]

Data were recorded as mean values ± SD (see Table 2). Treatment with CrPic and biotin significantly *reduced* fructosamine by 23.0 ± 56 mg/dL (p= 0.3698), as compared to placebo which *increased* by 12.9 ± 33 mg/dL (p= 0.5980); the comparison of the mean changes between treatment and placebo was p= 0.0263. Fasting glucose in the treatment group increased by 7.45 ± 65 mg/dL (p= 0.6597) as compared to placebo which increased by 50.19 ± 62 mg/dL (p= 0.0580); treatment vs. placebo was p= 0.0525. Insulin resulted in no significant change in either the treatment or placebo groups. AUCg *reduced* in the treatment group by 4701.8 ± 8959 min • mg/dL (p= 0.0441) but *increased* in the placebo group by 1649 ± 7013 min • mg/dL (p= 0.5702); treatment vs. placebo was p= 0.0264. OGTT at 30, 60, 90 and 120 minute intervals all decreased in the treatment group but the changes were not considered statistically significant according to p-values.[33]

Based on the statistical significance of decrease in fructosamine and AUCg levels vs. placebo and the lack of hypoglycemic events or serious ADRs in this study, the authors of this study recommended the use of CrPic and biotin supplements to enhance glycemic control.[33]

Albarracin et al study

This randomized, double blind, placebo-controlled trial[34] examined the effect of oral CrPic and biotin at improving glycemic control in overweight patients with uncontrolled, treated DMT2. Glycemic control was measured via serum HbA1c and fasting insulin and glucose levels. Secondary endpoints were effects on total cholesterol as well as the

cholesterol fractions HDL, LDL, and VLDL, triglycerides, and triglyceride:HDL ratio. The trial enrolled 447 subjects from 17 sites in the United States.[34]

Eligibility criteria consisted of patients who were overweight or obese (BMI ≥25 to <35 kg/m^2); between the ages of 18 and 70; a diagnosis of DMT2 according to ADA criteria for ≥1 year; poorly-controlled (HbA1c ≥7.0%); stable on OADs for ≥60 days prior to study entry; and fasting triglyceride level ≤400 mg/dL. Type, amount, and duration of OADs were not controlled for in the study. Exclusion criteria was extensive and consisted of the following: diagnosis of type 1 diabetes mellitus; hypoglycemic events requiring emergency transport ≤12 months; supplementation with CrPic within 90 days and/or any other form of chromium ≥120 µg/d within 30 days; daily insulin usage or rescue insulin usage >1 time per week; an incidence of DKA ≤12 months; creatinine, AST or ALT ≥2.0 x ULN; total bilirubin ≥1.5 x ULN; cardiovascular conditions requiring hospitalization ≤12 months; history of CVA, PE or unresolved DVT; uncontrolled high BP ≥160 mmHg systolic or ≥90 mmHg diastolic (seated); serious immunosuppressive disorder or current immunosuppressive therapy; disorders of the liver, thyroid, or kidneys or other disorders known to affect glucose or lipid metabolism; alcoholism or substance abuse; mental health issues that would prevent the subjects from completing the study; and women who were pregnant or nursing.[34]

Subjects were assigned 2:1 to either a treatment group in which they received 600 µg Cr^{3+} in the form of CrPic and 2 mg biotin, or a placebo group, with a study length of 90 days. As in the Singer et al[33] study, CrPic and biotin were administered as a single capsule manufactured under the name Diachrome® by Nutrition 21, Inc., Purchase, NY. Randomization occurred via standardized computer software. The study medication was randomized by personnel unaffiliated with the study from Nutrition 21, Inc., who kept

records of the randomization schedule and blinding codes. All study site personnel were blinded to which subjects received treatment.[34]

Both the treatment group and placebo group were balanced at study commencement with respect to demographics, ie, age, sex, race, weight, height, BMI and BP (p= 0.06 to 0.53). Of the 447 randomized patients at the study beginning, 78 (17.4%) were dropped or lost to follow-up, and an additional 21 had significant protocol violations not originally accounted for. Numerical differentiation data for loss to follow-up between the treatment and placebo groups were not presented; however, the authors stated there was no significant difference in attrition rates between the treatment and placebo groups.[34]

Data were collected on 348 patients considered eligible for analysis after these losses; 226 patients were assigned to the treatment group and 122 patients were assigned to the placebo group. Data were recorded as mean values ± SEM (see Table 2). Treatment with CrPic and biotin significantly reduced HbA1c by 0.54 ± 0.15% (p= 0.0001), as compared to placebo reduction of 0.34 ± 0.15% (p= 0.0001); treatment vs. placebo was p= 0.03. In a subset of study patients whose initial HbA1c was >10.0%, a much greater reduction of 1.76 ± 0.23% (p= 0.0001) was seen; placebo reduction in this group was 0.68 ± 0.30% (p= 0.006), and treatment vs. placebo in this group was p= 0.005. Fasting glucose overall was *reduced* by 9.8 ± 8.5 mg/dL (p= 0.002) as compared to placebo which actually *increased* by 0.7 ± 5.9 mg/dL (p= 0.84); treatment vs. placebo was p= 0.02. Fasting insulin resulted in no statistically significant change in either the treatment or placebo groups. Based on the statistical significance of these results and the lack of hypoglycemic events or serious ADRs, the authors of this study made recommendations for the use of CrPic and biotin supplements to further lower HbA1c.[34]

DISCUSSION

The goal of this systematic review was to explore the possibility that two OTC dietary supplements, CrPic and biotin, may further improve glycemic control in patients with DMT2 as adjunct therapy to prescription OADs. Two studies were found[33,34] that provide some evidence that these supplements may be effective.

A single combination supplement, Diachrome®, was tested in both the Singer et al[33] and Albarracin et al[34] studies. As of this writing, Diachrome® was no longer offered by Nutrition 21, Inc., and attempts to contact Nutrition 21, Inc. for more information on this supplement were unsuccessful. Although a 2012 study found that CrPic and biotin supplementation decreased serum glucose and in a diabetic rat model,[35] no human studies were found that tested both CrPic and biotin as separate supplements.

The patients in the Singer et al[33] and Albarracin et al[34] studies examined in this review, in which the supplement Diachrome® was used, did not experience serious ADRs or hypoglycemic events. This is in stark contrast to the numerous ADRs patients experience with the use of standard prescription OADs. For example, first-line prescription OAD treatment for a newly-diagnosed patient with DMT2 is either metformin or a sulfonylurea.[36] Between 20-30% of patients experience unpleasant gastrointestinal effects including nausea, vomiting, diarrhea and excess flatulence while using metformin.[18,37,38]

Prescription OADs offer an average of 1-2% reduction in HbA1c.[42,43] The Albarracin et al[34] study demonstrated modest overall HbA1c reduction of 0.54% and a substantial HbA1c reduction of 1.76% in those with baseline HbA1c >10.0%; these reductions are similar to those seen with prescription OADs. In both the Singer et al[33] and Albarracin et al[34] studies, ADRs that occurred with therapeutic doses of CrPic and biotin were not significant

and were not different from placebo. The lack of significant ADRs seen with CrPic and biotin use in both studies are promising results. Moreover, the FDA considers both CrPic and biotin to be generally recognized as safe (GRAS) dietary supplements, even at doses significantly higher than what were used in these studies.[44]

Although not specifically examined in this paper, it is interesting to note that the triglyceride:HDL ratio significantly reduced in the treatment groups in both the Singer et al[33] study (treatment vs. placebo p= 0.0453) and the Albarracin et al[34] study (treatment vs. placebo p= 0.05). Also, a statistically significant triglyceride level decrease was observed in in the treatment group in the Singer et al[33] study (treatment vs. placebo p= 0.0159). Changes in the other lipid values measured in both studies were not statistically significant from placebo.

Risk for potential bias was seen in both studies. Publication bias is a possible factor in both the Singer et al[33] and Albarracin et al[34] studies, due to the fact that funding was provided for both studies by Nutrition 21, Inc., maker of Diachrome®, the therapy in question. Referral bias may have occurred in the Singer et al[33] study since it was conducted at a single site and gave no details pertaining to how patient selection or recruitment occurred. Selection bias did not appear to play a significant role in either of the studies; the patient demographic data were not found to be dissimilar between the treatment and placebo groups. Attrition bias is in question for the Singer et al[33] study due to the fact that six out of the seven lost to follow-up were from the placebo group.

One important flaw concerning both studies was that neither controlled for amount or type of prescription OADs patients were taking at the beginning of the study. Prescription OADs were not considered statistically significant between treatment and placebo groups in

the Albarracin et al[34] study (p= 0.85); the Singer et al[33] study did not present these values. It is unknown if concomitant usage of OADs had an impact on the data, whether increasing or decreasing glycemic control effects obtained from CrPic and biotin use. Another important flaw in both studies was the small patient sample size, having been n= 43 and n= 447 in the Singer et al[33] and Albarracin et al[34] studies, respectively. These patient sample sizes may not be adequate for the results to relevantly apply to the vast diabetic population as a whole.

The duration of the Albarracin et al[34] study (90 days) was sufficient enough to obtain post-treatment HbA1c results. Although the OGTT was considered the gold standard for measurement of glycemic control, it has largely been replaced clinically by HbA1c; HbA1c gives the value of blood-glucose levels over the prior 2-3 months.[45-47] HbA1c was not used in the Singer et al[33] study because the study duration was 30 days; as a consequence, plasma fructosamine was used post-treatment for data collection due to the fact that it will provide a blood-glucose value for the prior 2-3 weeks.[48] Similar to HbA1c, fructosamine gives a reasonable estimation of blood glucose, though fructosamine measures glycated serum proteins, as opposed to HbA1c which measures glycated serum hemoglobin. Fructosamine measurement does not provide an exact correlation to HbA1c, but it can be used as a rough surrogate marker for HbA1c.[45,46,49]

Unfortunately the studies did not use the same patient inclusion and exclusion criteria. Inclusion criteria was very similar between studies; however, while the exclusion criteria was limited in the Singer et al[33] study, it was extensive in the Albarracin et al[34] study. This may be overlooked considering the Singer et al[33] study was the first study of its kind in humans, and was deemed a “pilot” study by the authors. It was apparent that the Albarracin et al[34] study was designed to further investigate the effects of CrPic and biotin based on the

results of the Singer et al[33] study. Both studies show promise, but again are limited because of their origination and small patient sample sizes.

CONCLUSION

The vast majority of the 20 million diagnosed diabetic adults in the U.S. have DMT2, which is associated with numerous physical health complications and a substantial economic burden. In addition to lifestyle changes, prescription OADs are beneficial in order to improve glycemic control, but for many the existing OADs are not sufficient. The combination of CrPic and biotin appear to have a modest impact on glycemic control improvement, but may have a larger benefit for those with an HbA1c of >10.0%. Based on the GRADE criteria used to evaluate the studies reviewed, the overall combined quality is low, and only a weak recommendation can be made for adjunct therapy of CrPic and biotin supplementation to improve glycemic control. However, considering the safety of CrPic and biotin, the evidence obtained from prior animal studies, the lack of significant ADRs and modest-to-substantial blood-glucose reducing effects seen in the two studies reviewed herein, it appears that CrPic and biotin supplementation as adjunct therapy to prescription OADs can be clinically justified. These results are promising, and warrant further investigation via additional randomized controlled studies using larger patient sample sizes, into the use of these seemingly benign and to some extent effective DMT2 therapies.

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TABLE 1. Characteristics of Reviewed Studies, GRADE profile

Study	*Design*	*Downgrade Criteria*					*Quality*	*Importance*
		Limitations	*Indirectness*	*Imprecision*	*Inconsistency*	*Publication bias likely*		
Fructosamine								
Singer et al[33]	RCT	No serious limitations	No serious indirectness	Serious imprecision[a]	No serious inconsistencies	Bias likely[b]	Low	Critical
AUC glucose								
Singer et al[33]	RCT	No serious limitations	No serious indirectness	Serious imprecision[a]	No serious inconsistencies	Bias likely[b]	Low	Critical
Fasting Glucose								
Singer et al[33]	RCT	No serious limitations	No serious indirectness	Serious imprecision[a]	No serious inconsistencies	Bias likely[b]	Low	Important
Albarracin et al[34]	RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	Bias likely[b]	Moderate	Important
Fasting Insulin								
Singer et al[33]	RCT	No serious limitations	No serious indirectness	Serious imprecision[a]	No serious inconsistencies	Bias likely[b]	Low	Important
Albarracin et al[34]	RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	Bias likely[b]	Moderate	Important
HbA_{1c}								
Albarracin et al[34]	RCT	No serious limitations	No serious indirectness	No serious imprecision	No serious inconsistencies	Bias likely[b]	Low[c]	Critical

[a]Singer et al[33] study had a small sample size (n= 36); short study length of 30 days therefore HbA1c could not be measured

[b]Singer et al[33] study, Albarracin et al[34] study: funded by the manufacturer of the chromium picolinate/biotin supplement that was tested

[c] Albarracin et al[34] study graded low for HbA1c due to the fact that it was the only study that measured this outcome

TABLE 2 Summary of findings

Summary of Findings						
Glycemic Control Marker	*Study*	*Number of Patients*		*Effect*		
		Treatment (total)	*Placebo or no treatment (total)*	*Improvement compared to baseline*	*p- value*	*p-value vs placebo*
Fructosamine	Singer et al[33]	20	16	-23.0 mg/dL	0.0263	0.0263
	Albarracin et al[34]	226	122	N/A	N/A	N/A
AUC glucose	Singer et al[33]	20	16	-4701.8 min • mg/dL	0.0441	0.0264
	Albarracin et al[34]	226	122	N/A	N/A	N/A
Fasting Glucose	Singer et al[33]	20	16	+7.45 mg/dL	0.6597	0.0525
	Albarracin et al[34]	226	122	-9.8 mg/dL	0.002	0.02
Fasting Insulin	Singer et al[33]	20	16	+0.005 µU/mL	0.9957	0.7772
	Albarracin et al[34]	226	122	+0.5 µU/mL	0.25	0.9
HbA1c	Singer et al[33]	20	16	N/A	N/A	N/A
	Albarracin et al[34]	226	122	-0.54%	0.0001	0.03